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Request for grant of a patent

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1.	Your reference	JHB/03245/JLH
2.	Patent application number *(The Patent Office will fill in this part)*	0313604.1
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	Britannia Pharmaceuticals Limited 41-51 Brighton Road Redhill Surrey RH1 6YS
	Patents ADP number *(if you know it)*	05621230002
	If the applicant is a corporate body, give the country/state of its incorporation	GB
4.	Title of the invention	DELIVERY DEVICE FOR POWDERED MEDICAMENT
5.	Name of your agent *(if you have one)*	BROOKES BATCHELLOR LLP
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	102-108 CLERKENWELL ROAD LONDON EC1M 5SA
	Patents ADP number *(if you know it)*	08142291001 ✓

		Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	-	-	-

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* — Yes
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Description	8
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Abstract	-
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Priority documents	-
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Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature Brookes Batchellor Date 11 June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom John Blake 01892 510600

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DELIVERY DEVICE FOR A POWDERED MEDICAMENT

The present invention is concerned with an delivery device for a powder, typically as an aerosol. The delivery device may be used for administering powder medicaments to body cavities, body surfaces or body organs. By way of example only, the device may be used administering powders for inhalation by asthma sufferers, and to treat other respiratory disorders.

The medicaments employed in inhalation devices are generally finely-divided dry powders having a particle size distribution which is small enough to be introduced into the airways and, preferably, deeply into the lungs in a gas stream from a dispersion device. Suitable dispersion devices may employ a propellant such as a halocarbon to form the gas stream and may include a tapered discharge nozzle baffle or a venturi to accelerate particles through a discharge nozzle, and to remove oversized particles. Suitable halocarbons include hydrofluorocarbons, hydrofluorochlorocarbons and fluorochlorocarbons having a low boiling point, such as those marketed under the trade mark "Freon".

The medicament may be packaged with a propellant in a pressurised aerosol container within the inhaler. US Patent 6,482,391, the subject matter of which is incorporated herein by reference, discloses a delivery device comprising a removable chamber for holding a powdered asthma medicament, a replaceable container of carrier gas, an inlet for introducing the carrier gas into the chamber and an outlet for discharging aerosolized powder from the chamber. Other inhalers have an impeller which mixes the powder into an air stream and delivers the powder-laden air into the patient's airways e.g. US Patent 5,577,497.

In one aspect the present invention provides a delivery device for a powdered medicament comprising a housing having

- a first chamber for a gas source,
- a second chamber for a container holding powdered medicament,
- •• the first chamber having an end portion with a gas outlet passage for transfer of carrier gas from the canister,

•• the second chamber having an end portion with an inlet passage for introducing carrier gas into the container, the inlet passage having an extension portion to lead carrier gas below the surface of powder within the container, and an outlet passage for discharging aerosolised powder from the container, the outlet passage having an extension portion to lead aerosolised powder to a delivery location, and

• a fluid passage connecting the outlet passage of the first chamber end portion with the inlet passage of the second chamber end portion.

The container holding powdered medicament can be of any suitable packaging, for example, a glass or plastic vial. The vial may then inserted in the second chamber so that the extension of the outlet passage enters the body of the vial, and the mouth of the vial is brought into a fluid-tight engagement with the end portion, preferably via a gasket or sealing ring. The vial may be held in engagement with the end portion by a screw or twist connection between the mouth of the vial and a connector fitting formed on the end portion, or by a closure for the other end of the chamber, the closure supporting the base of the vial and pressing the mouth of the vial against the end portion. The vial may contain a single dose for one-time use, or sufficient powder for several doses.

The canister of carrier gas or propellant may also be held in the first chamber with its gas outlet in fluid-tight engagement with the gas inlet member by a screw, twist or push connection between the container and the member, or by a closure for the other end of the chamber, the closure supporting the base of the canister. Preferably the connection is such that the metering valve of the canister is actuated to discharge gas by user pressure on the base of the canister.

The outlet for powder and carrier gas may exit into a delivery fitting appropriate to the intended site of delivery for the powder. For example the outlet may be shrouded with a mouthpiece which is a comfortable shape for the patient to place in the mouth. However the device is not restricted to delivery of powder by inhalation or to treat pulmonary disorders. For veterinary use the outlet may be extended to form, or connect to, a tracheal tube. For parenteral use, the outlet may be extended to for, or be connected to, a catheter. Powder medicaments are of value when administered, for

example, to buccal, oral, aural, rectal, occular, vaginal and nasal cavities. The chamber outlet may be used, or adapted for use, for delivery of powder to any body cavity or surface, or parenterally, for local or systemic effect.

In the present invention the powder container is suitably a removable vial containing powdered medicament, such as a lyophilized powder. In use, carrier gas passes through the fluid passage connecting the outlet passage of the first chamber end portion with the inlet passage of the second chamber end portion, and then via the extension tube into the powder in the vial. This allows the carrier gas to fluidise and levitate the powder within the vial, and ultimately to aerosolise the powder so that it is swept from the vial by the carrier gas through the outlet passage. Preferably the gas delivery extension tube is perforated along its length so that gas bleeds from the main stream in the tube and is ejected into the body of the vial to assist in levitation of the powder

Accordingly in another aspect the present invention provides a delivery device for a powdered medicament comprising:

- a chamber holding powdered medicament,
- an inlet for introducing a carrier gas into the chamber,
- an outlet for discharging aerosolized powder from the chamber,
- a source of carrier gas;

characterized in that the carrier gas is introduced into the chamber through

- a delivery tube extending from the inlet through the chamber and terminating in a gas exit aperture adjacent where in use it will be covered by the powder, so that the carrier gas can suspend the powder for discharge through the outlet,
- the delivery tube having one or more perforations in the portion extending through the chamber so that a portion of the delivery gas is discharged through the perforations into the body of the chamber to assist in suspension of the powder.

Additionally or alternatively, the exit aperture of the gas delivery tube may be directed relative to the walls of the chamber/vial so as to produce a circular flow of gas within the chamber. This again assists in levitating the powder and promoting aerosolisation by causing collisions among the powder particles and with the chamber

walls. For example the exit aperture may be positioned close to, and parallel with, the chamber walls. Suitably the chamber is cylindrical, with the exit aperture of the gas delivery tube positioned so that the gas flow is initially discharged substantially tangentially to the chamber walls to accentuate the formation of a vortex in the chamber.

The delivery tube may extend through the chamber at an inclined angle to the base of the chamber to increase the length of delivery tube in the chamber relative to the chamber height and so increase the number of perforations in the tube for a given unit spacing. Most suitably the delivery tube is given a helical shape within the chamber. The delivery tube is preferably positioned adjacent the walls of the chamber with the perforations directed into the body of the chamber, so that the jets of gas from the perforations are directed into the cylindrical space defined by the helix and interact with each other. Additionally further perforations may be directed towards the chamber walls if needed.

Further assistance to aerosolisation/suspension of the powder may be provided by vibrating the chamber. This may be achieved, for example, by positioning a vibrating membrane in contact with the base of the chamber.

Examples of devices constructed in accordance with various aspects of the invention is shown in the accompanying drawings, in which:
Figure 1 is a cross-sectional side view of a device in accordance with one aspect of the invention;
Figure 2 is a plan view of the device shown if Fig. 1;
Figure 3 is an extract from an unpublished poster presentation detailing the challenges faced in the delivery of a dry powder surfactant for the treatment of equine asthma and the use of a device as shown in Figures 1 and 2;
Figure 4 is an another from unpublished poster presentation detailing the outcomes of the delivery of a dry powder surfactant for the treatment of equine asthma using the device shown in Figures 1 and 2;
Figure 5 is a cross-sectional side view of a device in accordance with another aspect of the invention;

Figure 6 is a fragmentary view of the interior of a powder chamber provided within the device of Fig. 5.

One embodiment of a dispenser of this invention is shown in Figures 1 and 2 of the accompanying drawings. This embodiment has a housing (50) in the form of two cylinders (51,52) mounted side by side and forming respective chambers to hold a canister of pressurised propellant (not shown) and a vial (54) of powdered medicament.

The linked cylinders (51,52) are capped by a end portions (55,56) which in the embodiment shown are formed as a single surface of a unitary housing comprising linked cylinders (51,52) and their end closures (56,56). The other end of each cylinder is left open to allow insertion of the propellant canister and powder vial.

A passage way (57) bored through the plane of the end portions (55,56) links an inlet (58) for propellant formed in the end portion (55) and an aperture (59) formed in the end portion (56). The aperture (59) is plugged with a connector (60) which is formed internally with a passage (61) providing a pathway from passageway (57) into the interior of cylinder (52) and a passage (62) providing a pathway from the interior of cylinder (52) to the exterior of the end portion (56). A delivery tube (63) is inserted into the passage (61) and extends into the interior of the cylinder (52). The passage (62) links to an outlet port (64) on the outer surface of the connector (60).

The propellant canister is provided as a replaceable unit, and most suitably contains a compressed gas as propellant, such as carbon dioxide or air. However other conventional propellants, such as a low boiling liquid, preferably a fluorocarbon such as HFA-134a or HFC-227, under sufficient pressure to maintain the propellant liquid at normal room temperature, may also be used . The vial (54) containing powdered medicament, is also typically supplied as a sealed unit, so that the housing can be used for repeated delivery.
The propellant canister (53), is a conventional pattern which has a protruding valve stem, which when depressed releases propellant through a passage way in the valve stem. In use of the device, the canister is inserted into the cylinder (51) so that the

valve stem is located in the passageway (58). The passageway (58) is dimensioned so that the valve stem is a press fit in the passageway (58) and so holds the canister (53) in the interior of the cylinder (51).

Vial (54) has an opening (65) which before use is sealed to protect the powder contents. After stripping the seal, the vial (54) is introduced into the interior of the cylinder (52), so that the opening is forced against a resilient gasket (66) which encircles the aperture (59) in end portion (56). and the delivery needle (63) enters into the body of the vial (54). In this way the interior of the vial (54) is accessible to the passage ways (61) and (62) in the connector plug (60). The open end of the cylinder (54) can be closed with a screw threaded end cap (67), by which the vial (54) can be maintained in position with the opening (65) sealingly engaged with the gasket (66).

To use the device, the user pushes the end of the canister (53) into the interior of the cylinder (51). As the valve stem of the canister remains secured in the passage (58), the inward movement of the canister effectively depresses the valve stem, and releases propellant through the valve stem into the passageway (57). The open end of the passageway (57) is blocked by a grub screw or other seal (68), so the propellant exits via passage (62) and delivery tube (63) into the body of vial (54). The delivery tube is dimensioned so that its outlet tip (69) reaches into the powder contents of the vial (54). As a result the propellant discharges into the powder, and agitates, fluidises and aerosolises the powder contents of the vial (54). The propellant exits the vial (54) via the passage (61) and into the outlet port (64). The exiting propellant carries with it the aerosolised powder contents of the vial (54).

The delivery tube (63) may be periodically perforated along its length so that a proportion of the propellant is directed into the body of the vial (54) as well as exiting from the outlet (64). This assists in maintaining the powder in suspension in the propellant.

The outlet port (64) may be formed as, or exit into, a mouthpiece or shaped end piece which is a comfortable shape to place in the mouth, nose or other body orifice of a patient. Alternatively the outlet (64) may be extended to form, or connect to, a

tracheal tube.

A dispenser as described above has been successfully used in experimental veterinary treatment of respiratory disorders using powdered blends of phosphatidyl choline and phosphatidyl glycerol, based on the medicament disclosed in the above-mentioned US Patent 6,482,391, as detailed in annexed Figures 3 and 4.

In Figures 5 and 6 of the accompanying drawings, another embodiment of a dispenser of this invention has a casing (1) which forms a container to hold a pressurised canister (2) and a powder vial (3). Canister (2) may contain a conventional propellant, such as a low boiling liquid, preferably a fluorocarbon such as HFA-134a or HFC-227, under sufficient pressure to maintain the propellant liquid at normal room temperature. More preferably, the canister contains a compressed gas as propellant, such as carbon dioxide or air.

Vial (3) contains the powdered medicament, and may be supplied as a sealed unit independently of the casing (1) and other components. Canister (2), which again may be a replaceable unit, has a release valve (4) which is engaged with the casing (1) so that finger pressure on the end (5) of the canister will cause propellant to be released into a tube (6). Tube (6) is typically a hard plastics, e.g. pvc or polypropylene, tube of about 2 to 3 mm outside diameter and about 0.5 to 2 mm inside diameter. Tube (6) connects valve (4) with an inlet (7) and thence to a helical delivery tube (8) which extends into the vial (3) as far as its base, so that its outlet end (9) is covered by powder (10) within the vial. Vial (3) may be closed with a rubber seal which is penetrated by the inlet (7).

The helical delivery tube (8) is periodically perforated along its length with secondary outlets (11) so that a small proportion of propellant is directed into the body of the vial (3) as well as exiting from the outlet (9). A second tube (12) extends part way into the vial (3) through the rubber seal in the neck of the vial and allows powder aerosolised within the vial (3) to exit with the propellant as a powder cloud that can be inhaled by a patient. For human use, the tube (12) may be formed as, or exit into, a mouthpiece which is a comfortable shape for the patient to place in the mouth. For

veterinary use the tube (12) may be extended to form, or connect to, a tracheal tube.

When the patient is in need of medication, the tube (12) or a mouthpiece is placed in the patient's mouth and the canister (2) is depressed to open the release valve (4). This causes the propellant to enter the vial (3) via the delivery tube (8). The primary outlet for the propellant is at the end (9) of the tube (8). The outlet (9) is placed alongside the wall of the cylindrical vial (3) so that the propellant issues in a direction that would be substantially tangential to the wall in the absence of the constraining effect of the wall. The wall causes the propellant to follow a circular path which has a swirling effect on the powder (10) within the vial (3). As a result the powder is suspended in a vortex as it moves towards the outlet tube (12). This improves the aerosolising effect due to the propellant/powder and powder/powder contact before the powder is discharged from the tube (12) for inhalation.

As the vortex is created, further propellant is discharged from the secondary outlets (11) and this assists in maintaining suspension of the powder in the propellant stream. Additional assistance may be provided by positioning a vibrator (13) in contact with the housing (1) or vial (3), so that vibrations are transmitted to the vial (3) and its powder content (10).

The result is that a cloud of aerosolised powder medicament is dispensed into the patient's airways. Connector fittings (14,15) may be provided at elbow points instead of using curved tubing. The connectors (14,15) may include valves set to permit measured quantities of propellant to enter the vial to suit specific patients or specific medicaments. Similarly, valve (4) may be set to release when the pressure in the vial (3) reaches a predetermined level.

For human use, especially for a device intended for self-administration, the housing (1) is preferably provided as an easy-to-hold unit as disclosed in the same US Patent 6,482,391.

The helical gas delivery tube (8) shown in Figure 6 may also be used as a replacement for the needle-like tube (63) shown in Figure 1.

CLAIMS

1. A delivery device for a powdered medicament comprising a housing having a first chamber (51) for a removable canister of carrier gas (53) and a second chamber (52) for a container (54) holding powdered medicament; the first chamber (51) having an end portion (55) with a gas outlet passage (58) for transfer of carrier gas from the canister (53); the second chamber (52) having an end portion (56) with an inlet passage (61) for introducing carrier gas into the container (54), the inlet passage (61) having an extension portion (63) to lead carrier gas below the surface of powder within the container (54), and an outlet passage (62) for discharging aerosolised powder from the container (54), the outlet passage (62) having an extension portion (64) to lead aerosolised powder to a delivery location; and a fluid passage (57) connecting the outlet passage (58) of the first chamber end portion (55) with the inlet passage (61) of the second chamber end portion (56).

2. A delivery device according to claim 1 in which the end portions (55,56) are linked together and the fluid passage (57) is incorporated within the linked end portions.

3. A delivery device according to any preceding claim in which the inlet passage (61) and the outlet passage (62) are formed in a connector plug (60) located in an aperture (59) in the end portion (56).

4. A delivery device according to any preceding claim in which each of the chambers (51,52) is a hollow cylinder.

5. A delivery device according to claim 4 in which the cylinders are fused together side by side.

6. A delivery device according to any preceding claim in which the extension portion (63) is a perforated tube.

7. A delivery device according to any preceding claim in which the removable canister of carrier gas (53) is a canister with a metering valve having a hollow valve stem for discharge of gas and the valve stem is a press fit in the gas outlet passage (58) in the first chamber end portion, and the powder container (54) is a vial whose open mouth is in fluid-tight engagement with the second chamber end portion (56) via a gasket or sealing ring, and is held in engagement with the end portion (56) by a closure (67) for the other end of the second chamber (52), the closure (67) supporting the base of the vial (54) and pressing the mouth of the vial (54) against the end portion (52).

8. A delivery device for a powdered medicament substantially as described herein with reference to Figures 1 and 2 of the accompanying drawings.

9. A delivery device for a powdered medicament comprising
a chamber (3) for holding the powdered medicament (10);
an inlet (7) for introducing a carrier gas into the chamber (3);
an outlet (12) for discharging aerosolized powder from the chamber (3);
a source (2) of carrier gas; characterized in that the carrier gas is introduced into the chamber (3) through a delivery tube (8) extending through the chamber (3) and terminating in a gas exit aperture (9) adjacent the base of the chamber (3), where before use it will be covered by the powder (10), so that the carrier gas can aerosolize the powder (10) for discharge through an aerosol outlet aperture (12) positioned in the chamber (3) above the level of the powder (10) before use;
the delivery tube (8) having one or more perforations (11) in the portion extending through the chamber (3) so that a portion of the delivery gas is discharged into the body of the chamber (3) to assist in suspension of the aerosol.

10. A delivery device according to claim 9 in which the exit aperture of the gas delivery tube is directed relative to the chamber walls so as to produce a circular flow of gas within the chamber.

11. A delivery device according to claim 10 in which the chamber is cylindrical, with the exit aperture of the gas delivery tube positioned so that the gas flow is

initially discharged substantially tangentially to the chamber walls.

12. A delivery device according to any preceding claim in which the chamber is a removable vial containing powdered medicament, such as a lyophilized powder.

13. A delivery device according to any preceding claim in which the source of carrier gas is a removable container of pressurized gas

14. A delivery device according to any preceding claim in which the delivery tube extends through the chamber at an inclined angle to the base of the chamber.

15. A delivery device according to any preceding claim in which the delivery tube has a helical shape within the chamber..

16. A delivery device according to any preceding claim in which the delivery tube is positioned adjacent the walls of the chamber with the perforation(s) directed into the body of the chamber.

17. A delivery device according to any preceding claim in which the aerosolisation or suspension of the powder is supplemented by a vibrator which vibrates the chamber.

18. A delivery device for a powdered medicament substantially as described herein with reference to Figures 3 and 4 of the accompanying drawings.

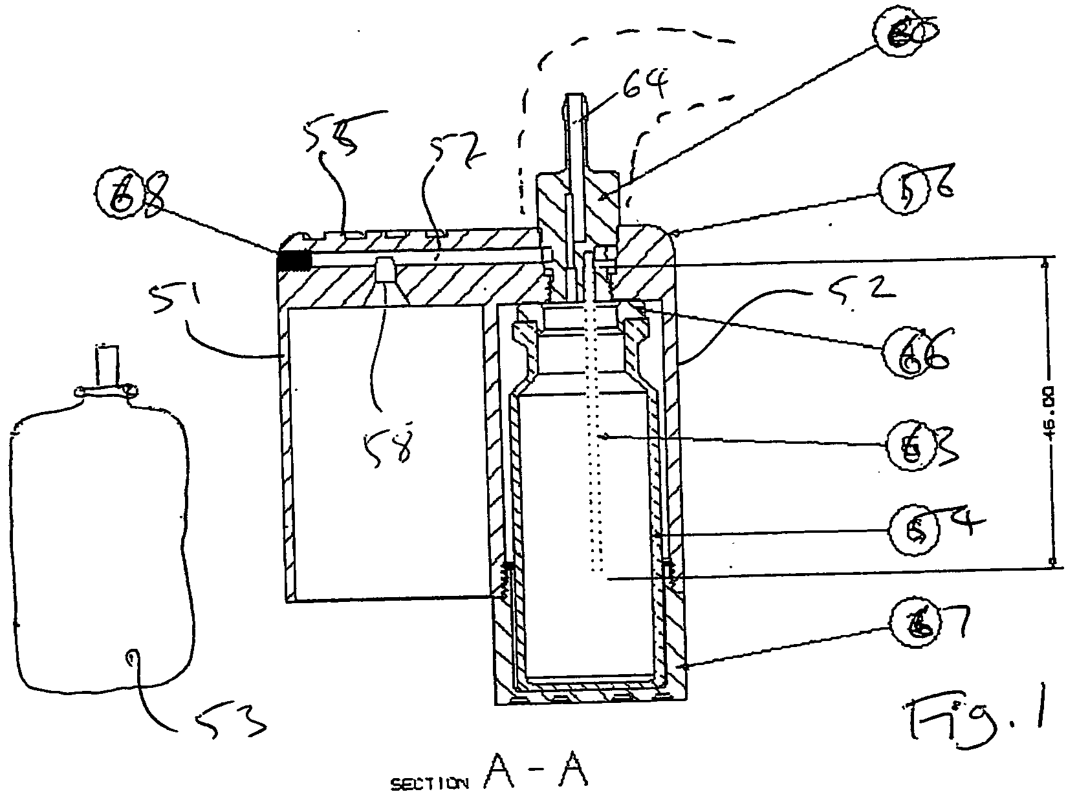


Fig. 1

Fig. 2

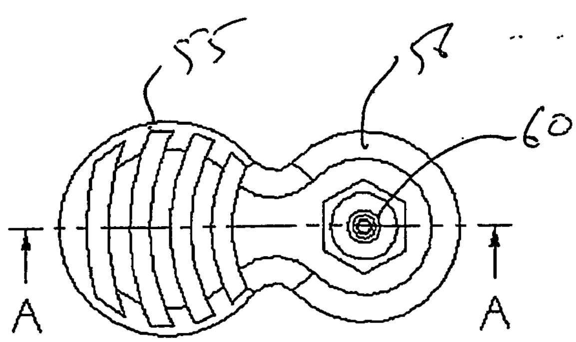


Fig. 3.

THE CHALLENGES

PRIMARY RESEARCH GOALS:

>To investigate the use and approach for the delivery of a thermally labile, hygroscopic and 'dry surfactant' ensuring acceptable physicochemical character.

>To eliminate proximal deposition in the nasopharynx and trachea using a novel hand held system, to an equine model in a clinical field setting.

>To deliver high doses of respirable material contrary to current perception and practice.

> To observe the effect of a dry powdered surfactant on the inflamed equine airway.

WHY CHOOSE AN EQUINE RESPIRATORY MODEL?

Horses are susceptible to a plethora of respiratory complaints. Heaves is the equine equivalent of asthma and both diseases share similar aetiology and pathology. The disease, in the equid, has been shown to proceed via Th_2 cytokine driven mechanisms. [1] They, like their human counterparts, have poor compliance and a massive lung surface area estimated to be in the region of 1000m^2

TO INVESTIGATE THE USE AND APPROACH FOR DELIVERY OF A THERMALLY LABILE, HYGROSCOPIC AND 'DRY SURFACTANT' ENSURING ACCEPTABLE PHYSICOCHEMICAL CHARACTER.

The Surfactant

Pumactant, (formally known as ALEC), is a mixture of two phospholipids: DPPC and PG in a ratio of 7:3 DPPC:PG. This specific ratio of phospholipids has a low phase transition temperature (approx..32°C) which it is believed facilitates rapid spreading at body temperature when in contact with an air water interface. It is also highly rich in DPPC which mimics the high percentage of endogenous DPPC in -vivo.

Rationale for Use As a 'Dry Powder'

In a previous human (allergic asthma) study[2], Pumactant had been delivered as a dry powder and produced excellent clinical results. Currently, surfactants are delivered as aqueous based preparations, however it is has been demonstrated that surface activity is reduced when the active is delivered as an aqueous suspension. Indeed, delivery of aqueous preparations is counterintuitive in certain disease states: RDS.

Physical Stability of the Treatment

The material is physically unstable even at conditions of low relative humidity approx. 30%, and it can undergo morphological changes,which may affect particle size, as is shown in the S.E.M's below. Figure 1(a) shows material which has been stored at 2 - 8°C; approx 10% R.H, and Figure 1 (b) is material which has been stored at 15 - 30°C and approx 30 -60%R.H. Careful attention must therefore be applied to storage and delivery of the surfactant.

Figure 1: **SEM Micrographs of Pumactant Stored at (A) 2 - 8°C (~10% R.H), and (B) 15 - 30°C (30 -60%R.H).**

TO ELIMINATE PROXIMAL DEPOSITION IN THE NASOPHARYNX AND TRACHEA USING A NOVEL HAND HELD SYSTEM, TO AN EQUINE MODEL IN A CLINICAL FIELD SETTING.

The Fundamental Issues

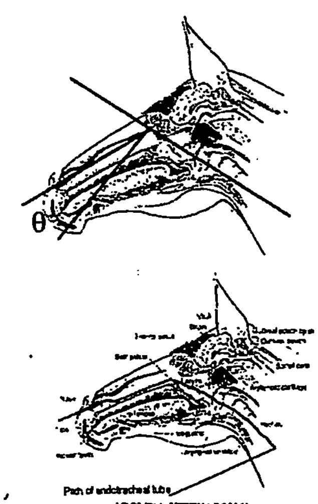
The main issues with respiratory drug delivery to the equid lung focus on differences in anatomy and physiology of the species; as with their human counterparts, substantial drug losses occur in proximal lung regions. Horses are obligate nasal breathers, so problems are exacerbated by restrictions of airflow in nasal turbinates. In fact, the nasal passages in the equid account for 80% of the total resistance to airflow. When coupled with conditions such as DDSP and laryngeal hemiplegia such factors may significantly reduce not only aerosolised drug therapies but respiratory gas transport. Pragmatically, we decided to circumvent the problem by utilising an endotracheal tube, bypassing the nasal anatomy, delivering the material to each bronchus; this arrangement, obviously,would also omit patient compliance issues. Table 1, below, illustrates some selected differences in human-equine anatomy and physiology, while Figures 2(a) and 2(b) illustrate the path of the delivery tube.

Table 1: **A Comparison of Selected Physiologic and Anatomic Parameters of the Human and Equine Species**

PARAMETER	HOMINID	EQUID
Tracheal Length/cm	12	75
Tracheal Diameter/cm	1.8	5
Primary Bronchi Diameter/cm	1.2	3.3*
Volumetric flow rate Cm3s-1	233.3	2800
Tidal Volumes cm3	500	5600
Breathing frequency	14	15
Minute Volume (L)	7	78
Drug Dosage (mg)	800**	2400***

* = Estimated diameter
** = Actually delivered in a human asthma trial
*** = Calculated from theory

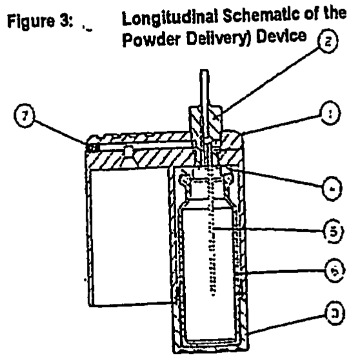
Figure 2: **Longitudinal Sections of the Equine Skull (A) Indicating Anatomy and (B) the Path of the Endotracheal Tube**



The Delivery Device

The schematic diagram below (Figure 3) shows the delivery system utilised to generate the aerosol. The system was developed around the principle of fluid bed generation, and once the powder was fluidised it was subsequently entrained in the flow of carrier gas.
Chamber 1 houses a disposable pressurised carbon dioxide source, and chamber 2 the vial of surfactant.

Figure 3: **Longitudinal Schematic of the Britannia PADD (Pressurised Aerosol Dry-Powder Delivery) Device**



Part Number	Description
1	Device Body
2	Connecting nu
3	Base Cap
4	Sealing gaske
5	Delivery Tube
6	Medicament

FIG. 4.

THE OUTCOMES

TO DELIVER HIGH DOSES OF RESPIRABLE MATERIAL CONTRARY TO CURRENT PERCEPTION AND PRACTICE.

The use of an equine model, as previously described, facilitated the delivery of a mass of powder not conventionally delivered to the respiratory tract in a unit dose. The device and mode of delivery is erstwhile described, but what is not apparent is the particle size distribution of the material used. Since it was manufactured as freeze dried powder the particle size distribution does not conform to conventional respiratory p.s.d's. In fact, the MMAD as evaluated by laser diffraction was approx 10 microns with a distribution that ranged from approximately 1 to 180 microns. This was initially a concern. Current practice delivers particles in a 2-5 MMAD micron range and, whilst direct delivery to each bronchus removed some proximal deposition, it had not been established the extent to which a large particle would penetrate.

The theoretical deposition was calculated by manipulating established equations, [3] which although were primarily developed for human subjects served to illustrate the impaction in the turbinates and trachea. In addition, a series of in-vitro measurements were conducted using an Andersen cascade impactor. To simulate the clinical procedure, the cascade throat was bypassed, and the endotracheal tube was situated in line with the cone proximal to the cascade The calculated depositions for equid are given in Table 3, taken from equation 1, and the in-vitro Andersen cascade results are given in Figure 4.

$$P(i) = 1 - \exp(-4e/\pi) \qquad \text{Equation 1}$$

$P(i)$ = the probability of impaction of a particle experiencing turbulent airflow.
(The Reynolds number for airflow through the nasal passage and trachea indicated turbulent flow)

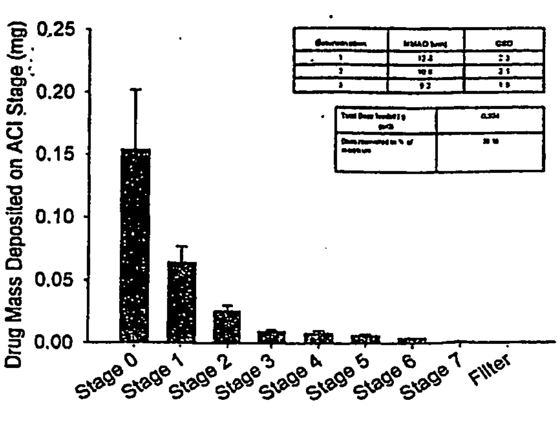
Where $e = \theta(i)\,\tau\,U(i)/D(i)$ and $\theta(i)$ = angle of bend of generation (i) with respect to the horizontal., $U(i)$ = mean velocity of air in generation (i), τ = particle relaxation time (product of particle mobility and mass) and $D(i)$= diameter of generation airway (i).

Table 2: Theoretical Deposition Probabilities of Aerosolised Particles in the Equine Nasal Turbinates and Trachea.

Particle size	Deposition Probability*
MMAD	Equid
One Micron	0.0038
Ten Microns	0.287

* Assuming both a ventral nasal meatus and tracheal diameters of 5cm (a continuous pipe) and a head tilt angle of 30degrees as shown in Fig.2(b)

Figure 4: The In-vitro Assessment of Pumactant Aerosolised and Delivered via a 1.5m Long 1mm Diameter Endotracheal Tube



RESULTS

The initial baseline assessment from tracheal washings are given in Table 3.

Table 3. Baseline Assessment of Subject Prior to Study Start

Macroscopic appearance		Microscopic appearance	
Mucus	+++	Neutrophils	+++
Cloudy	trace	Deg Neutrophils	+
Blood	+	Macropahges	+
		Siderophages	+
		Epithelium	++

General Inflammation score (0-12) 7
Scoring severity --- = non detected, + = mild, ++++ = severe

The results during the term of the study are illustrated in Table 4.

Table 4. Tracheal Wash Data Collected During the Term of the Study

Date	Nucleated Cells / I Cell Type	Neutrophils	Mononuclear	Eosionphils	Epitheli
19.01.02 (24 hours post treatment)	0.3 x 109	—	—	—	—
26.01.02 (Pre treatment)	1.2 x 109	++	++	+	+
26.01.02 (24 hours post treatment)	0.8 x 108	+	++	—	++
22.02.02 centrifuged deposit smear cell density (Pre treatment)	HIGH	28%	24%	—	48%
25.02.0centrifuged deposit smear cell density (Post treatment)	LOW	32%	27%	3%	38%

DISCUSSION

This study, although investigational and located in a field setting, serves to illustrate th potential use of phospholipids in the treatment of equine respiratory disorders: Heaves in thi instance. The mechanism of action is at present unknown but, from the limited data in thi single case study and other unpublished in-vitro experiments, we infer a combination c physical and immunomodulatory mechanisms[4,5].

Primarily, the treatment is hypothesised to 'work above the line': to form a barrier over th epithelial surface it contacts with. The results from Table 4 indicate a reduction in epitheli shedding. When the epithelium is denuded or missing exposes the tissues below to insul allowing the cascade of subsequent inflammatory mechanisms to proceed.

The data collected in Tables 3 and 4 although limited, illustrates some interesting trends. Th number of neutrophils decreased during the first part of the study however fluctuated an slightly increased during the latter half. Such fluctuations could possibly arise from the fact th study was conducted in a field setting and a number of alternative parameters were not strict monitored or controlled.

CONCLUSIONS

The delivery of high dose medicaments to the equine respiratory tract is a technology yet to b realised. Initial studies have indicated that the use of Pumactant as a treatment for equin respiratory diseases (such as Heaves) shows great potential, clearly warranting furthe investigation

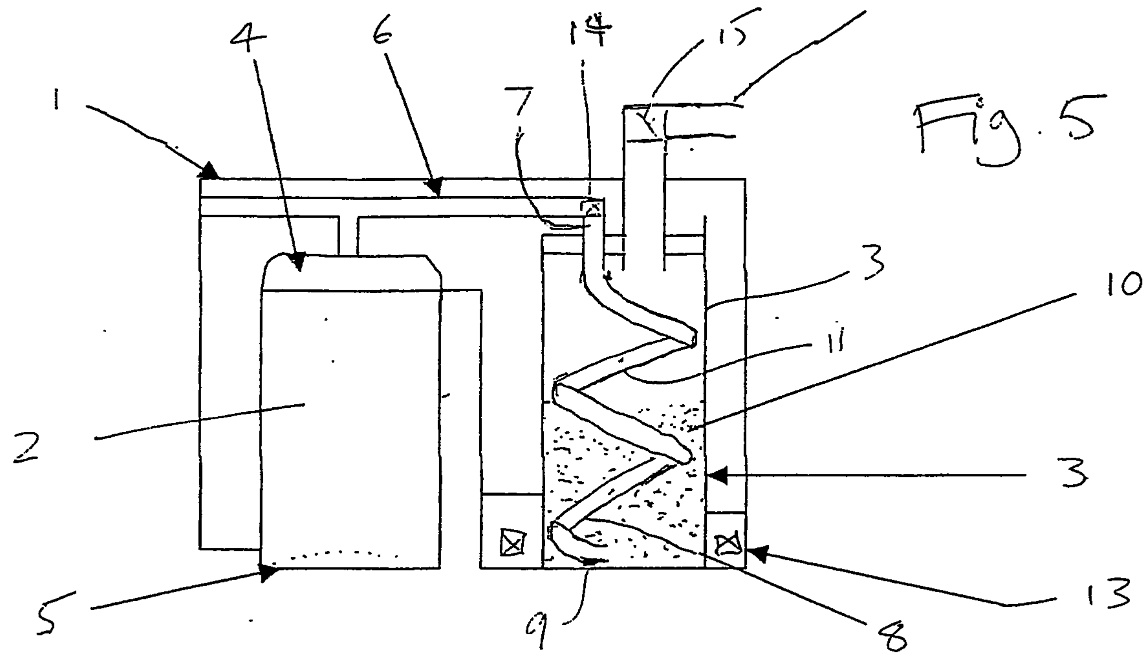


Fig. 5

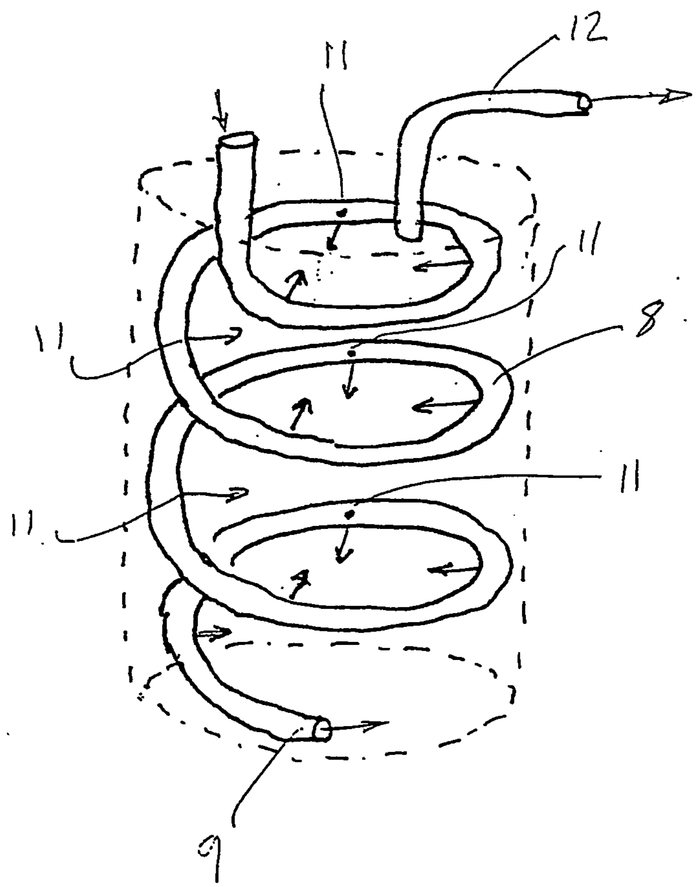


Fig 6

FIG. 7

The use of a novel 'active' inhalation device to deliver high respirable fractions of high dose dry powder active agents to the lung.

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INTRODUCTION

The use of dry powder inhalers (DPI) for the delivery of medicaments for respiratory disease has become popular in recent years. Such a move is mainly due to both the ease of use and chemical stability of the active in a solid form. Conventional DPI devices are based around the delivery of relatively low doses (<400 µg) of micron-sized material (<5 µm diameter). However to date, the delivery of higher doses applicable, for example, to vaccine delivery have not been investigated.

As part of an ongoing development program, a novel 'active' dry-powder inhalation PADD device (pressurised aerosol dry-powder delivery) has been developed for delivery of high dose (10-1000 mg) cohesive powders to the respiratory tract.

Preliminary in vitro studies have been undertaken using Pumactant™, an artificial lung surfactant, which has been shown to have a prophylactic effect (100 mg) in recent clinical trial studies[1]. Pumactant is a mixture, of dipalmatidylphosphatidylcholine and phosphatidylglycerol (DPPC and PG) and has similar properties to that of indigenous surfactant. However, due to such similarity, it has a low transition temperature, high affinity for moisture and is therefore is naturally cohesive. Clearly an ideal subject for study using the PADD active delivery system.

INTRODUCTION

Micronised Pumactant was first characterised for particle size and morphology. Particle size distribution was obtained by laser light scattering (Malvern Mastersizer X, Malvern UK) using a small volume dispersion cell and cyclohexane as a dispersant (samples were sonicated for 5 mins prior to analysis). Particle morphology was investigated using scanning electron microscopy at 10kV (JEOL 6310, Jeol, Japan).

A schematic diagram of the PADD device is shown in Figure 1. The PADD device is a handheld high-energy aerosolisation system utilising pressurised CO_2 gas (in this case) to supply a positive pressure (through a series of Venturi tubes) into a carrier-free powder bed. The aerosolised powder is entrained and inhaled through a conventional mouthpiece. Can pressure for the initial studies was 12bar, which lasted a duration of approximately 7 seconds.

For comparative purposes, aerosolisation efficiency of the active PADD device was compared to an off the shelf conventional DPI (Cyclohaler), using a twin stage impinger[2] (Copley Scientific, Nottingham, UK) at 60L.min^{-1}. Delivered dose and repeatability were investigated using the dose unit sampling apparatus[2] (DUSA) (Copley) at 30L.min^{-1}, while the influence of delivered dose on aerosol size distribution was investigated using the Anderson cascade impactor[2] (ACI) (Copley).

Drug content, obtained from the deposition studies were calculated by mass and HPLC (using a evaporating light scattering detector and validated method).

A representative photograph of the PADD active dry powder inhaler device, with conventional mouthpiece, CO_2 canister and large fill sample vial are shown in Figure 2 alongside a dissembled ACI with dose deposition post testing (with a ~100 mg Pumactant dose).

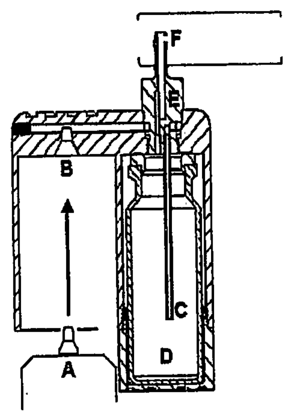
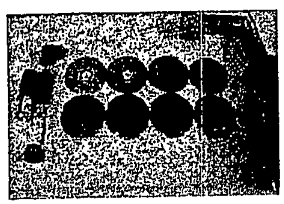


Figure 1. Schematic diagram of the PADD dry powder aerosolisation device. Where A. pressurised CO_2 canister, B. connection duct and transfer conduit, C. aerosolisation pipe, D. vial containing drug material, E. exit channel, F. PADD orifice and patient mouthpiece.

Figure 2 (right). Photographic image of the PADD aerosolisation device assembly and particle deposition pattern on Anderson cascade plates post analysis (~ 100 mg dose)



RESULTS AND DISCUSSION

A representative SEM image of the Pumactant with particle size distribution is shown in Figure 3. The micronisation process was conducted at low temperatures to avoid thermal transitions and the subsequent particulates appeared to be discrete entities with a median diameter of 1.49 µm ± 0.08 µm (n=3). However, the SEM images suggested the material to be highly agglomerated. Aerosolisation efficiency, measured using the a conventional Cyclohaler indicated that although the total delivery efficiency was relatively high (>60% for a 50mg loaded dose) no fine particle fraction of Pumactant was recovered from stage 2 of the TSI. Such observations suggest that the energy imparted by a non-active device is not strong enough to overcome particle cohesion. In comparison, initial TSI investigations using an non-optimised PADD device indicated a delivery efficiency of 64 % ± 21% with a FPF of 39% ± 14%.

Optimisation of the PADD device led to improved delivery efficiency and increased fine particle fractions. Depending on target dose, delivery efficiency was between 60 and 70% with relative standard deviations less than 6% (n>6).

Particle deposition profiles (Figure 4) obtained by ACI suggested similar particle deposition profiles (15, 33, 50 and 75 mg delivered dose), with a mean fine particle fraction (particles < 3.3 µm) across the delivered dose range of 54% ± 10%.

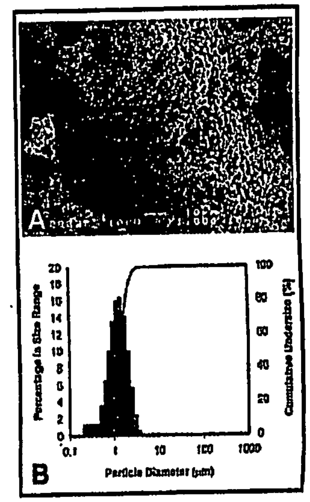


Figure 3. (A) Scanning electron micrograph of the micronised Pumactant and (B) Particle size distribution.

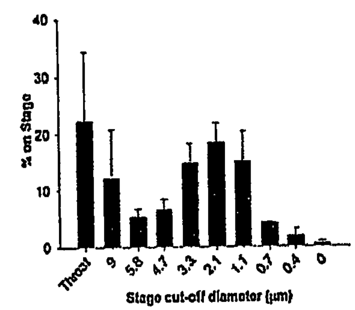


Figure 4. Mean percentage recovery for ACI deposition

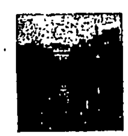
Conclusions

The delivery of high dose medicaments to the respiratory tract is a technology yet to be realised. Initial studies have indicated that when considering non-active devices the energy required to efficiently aerosolise such doses may not be feasible.

Preliminary studies, using a high dose asthma therapy drug, Pumactant and active dry powder inhaler (Britannia PADD device) have shown such goals to be possible.

References

1. Babu,K.S., Woodcock, D.A., Smith, S.E., Haminsley, A.M., Little, L., Staniforth, J.N., Holgate, S.T., and Conway, J.H. Pumactant abolishes early asthmatic response in patients with allergic asthma, Proceedings of the American Thoracic Society (2002)
2. Description of the TSI, DUSA and ACI apparatus can be found in the British Pharmacopoeia. Methods used through out the study followed the specific guidelines.



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